Remarks

Rejections pursuant to 35 U.S.C. § 103(a)

Claims 1 – 31 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Chu, *et al.,* (Infection and Immunity, 40(1):245-56, April 1983) (hereinafter "Chu") in view of European Patent Application No. 0 497 525, May 8, 1992 (the '525 publication). Applicants respectfully traverse this rejection.

At the outset, the applicants offer that the present invention provides a method of making a multivalent conjugate vaccine that induces high immunogenicity against pneumococcus while counteracting the well known effect of carrier-induced epitopic suppression (CIES). There are no teachings or suggestions in the art of how to do this.

The Office relies on Klein et al (Microbial Drug Resistance, 1(1):49-58, 1995) at page 53, Table 4, for the proposition that the ratio of carbohydrate to protein is a factor that influences the immunogenicity of conjugate preparations, concluding that it was known that the amount of carrier protein used could affect the immunogenicity of the conjugate preparations. Combined with the fact that the particular carrier proteins and polysaccharides recited in the pending claims were known, the Office concludes that it required only routine optimization to arrive at the claimed compositions. The applicants respectfully disagree for several reasons.

First, varying the ratio of carbohydrate to protein would not lead the ordinary artisan to the presently claimed composition. The claims do not merely recite specific ratios. Rather, the claims recite employing at least two different types of carrier proteins, one of which is Tt and another of which is Dt.

Second, while Klein teaches that the ratio of carbohydrate to protein is a factor that influences the immunogenicity of conjugate preparations, Klein teaches no more. Klein does not teach *how* the ratio influences immunogenicity. The Office assumes that by merely varying the ratio of protein to carrier in a routine manner one could obtain an effective vaccine. This is not supported by Klein or any other art of record.

Third, and perhaps most importantly, in focusing solely on Table 4 of Klein, the Office ignores other teachings of Klein that undermine the bases for rejection. In the section entitled, "Factors that Affect Conjugate Vaccines," Klein lists several factors complicating conjugate vaccine design and manufacture and rendering the results *a priori* unpredictable:

> A dose-response relationship exists between the carrier, saccharide, and host that affects immunological mechanisms impacting on the function of conjugate vaccines. This relationship may: (1) reduce vaccine effectiveness due to antigenic competition caused by an excess number of serotypes in the vaccine; (2) induce immune tolerance/suppression to epitopes associated with the carrier protein following repeated immunizations with conjugate vaccines; and (3) affect carrier priming as a result of prior or co-administration of unconjugated carrier proteins (e.g., diphtheria toxoid) that are often part of other childhood vaccines (e.g., DTP). High costs and technical difficulties in developing and manufacturing multivalent conjugate vaccines will impact further on the number of serotypes incorporated into such products, especially when they are designated for use in developing countries. Practical limits, thus, dictate that pneumococcal conjugate vaccines contain fewer serotypes than the conventional 23-valent polysaccharide vaccines. In this regard, it may be difficult to apply the success of the Hib conjugate vaccine to the improvement of the existing pneumococcal vaccine.

Klein at p. 51, cols. 1-2 (emphasis added). Thus, Klein recognizes the many difficulties and uncertainties associated with making an effective multi-valent pneumococcal vaccine and teaches that it would not be a matter of mere routine optimization. Rather, Klein teaches that the ordinary artisan would face numerous technical hurdles with no obvious way of overcoming them or even any degree of certainty that they could be overcome.

And Klein is not alone in these teachings. For example, WO 00/56360 (filed shortly after the present application; copy enclosed) teaches at pp. 7-8,

> A number of problems are associated with each of these commonly used carriers [including Dt and Tt], including in production of GMP conjugates and also in immunological characteristics of the conjugates.
>
> Despite the common use of these carriers and their success in the induction of anti polysaccharide antibody responses they are associated with several drawbacks. For example, it is known that antigen specific immune responses may be suppressed (epitope suppression) by the presence of preexisting antibodies directed against the carrier, in this case Tetanus toxin (Di John et al; (1989) Lancet, 2:1415-8). In the population at large, a very high percentage of people will have pre-existing immunity to both DT and TT as people are routinely vaccinated with these antigens. In the UK for example 95% of children receive the DTP vaccine comprising both DT and TT. Other authors have described the problem of epitope suppression to peptide vaccines in animal models (Sad et al, Immunology, 1991; 74:223-227; Schutze et al, J. 15 Immunol. 135: 4, 1985; 23 19-2322).
>
> In addition, for vaccines which require regular boosting, the use of highly immunogenic carriers such as TT and DT are likely to suppress the polysaccharide antibody response after several injections. These multiple vaccinations may also be accompanied by undesirable reactions such as delayed type hyper-responsiveness (DTH).
>
> …

> The selection of a carrier protein, therefore, for a polysaccharide based vaccine will require a balance between the necessity to use a carrier working in all patients (broad MHC recognition), the induction of high levels of anti- polysaccharide antibody responses and low antibody response against the carrier.
>
> The carriers used previously for polysaccharide based vaccines, therefore have many disadvantages. This is particularly so in combination vaccines, where epitope suppression is especially problematic if the same carrier is used for various polysaccharide antigens. In WO 98/51339 [the present application], multiple carriers in combination vaccines were used in order to try to get over this effect.

While WO 00/56360 was filed after the present application, these teachings accurately reflect the thinking in the art regarding Dt and Tt as carrier proteins and would have dissuaded one of ordinary skill in the art from developing new conjugate vaccines with either Dt or Tt, let alone both!

And these teachings are echoed by the prior-published de Velasco, Microbiological Reviews, 59: 591-603 (1995) (copy enclosed):

> Until now, proteins to be used as carriers in conjugate vaccines were selected on basis of their Th-cell-activating capacity. Following this approach, effective pneumococcal and other conjugate vaccines were constructed with well-known heterologous proteins like diphtheria or tetanus toxoids. However, an important disadvantage in using these carrier proteins might be the excessive production of anti-carrier Ab as a result of frequent immunizations in childhood. Anti-carrier Ab have been shown to suppress subsequent responses to conjugates in mice as well as in humans, an effect that has been attributed to FcγRII-mediated inhibition of Ab production. The risk of inducing suppressive amounts of anti-carrier Ab should not be underestimated, especially when dealing with polyvalent pneumococcal conjugate vaccines that contain multiple doses of carrier protein (one for each serotype included) in a single vaccine vial. Deletion of B-cell epitopes from these carrier proteins might be a method to overcome suppression while retaining Th-cell induction.

p. 599, cols 1-2 (emphasis added).

de Velasco and WO 00/56360 bracket in time the filing of the present application and demonstrate that at the time of filing the present application the wisdom in the art was to avoid Dt and Tt as pneumococcal vaccine polysaccharide carrier proteins.

The Office next argues that the use of multiple carrier proteins in the same composition was known to the art well prior to Applicants filing date, quoting Klein: "At the present time, all of the vaccine manufactures are aiming to produce pneumococcal conjugate vaccines that contain between seven and nine serotypes conjugated to one or several different carrier proteins."

The applicants respectfully submit that the Office has misconstrued this statement, which, when read in isolation, is ambiguous. The applicants submit that one of ordinary skill in the art would understand this statement to mean not that vaccine manufacturers were testing conjugate vaccines containing several different carrier proteins in the same vaccine but that any one particular manufacturer was either testing a single carrier protein in all its multivalent conjugate vaccines (e.g., CRM 197 by Praxis, *see* Table 6 of Klein) or that it was testing several carrier proteins, but each in a different vaccine (e.g., Tt and Dt by Pasteur/Merieux/Connaught, *see* Table 6 of Klein). That is, the reference to "seven and nine serotypes conjugated to one or several different carrier proteins" is a reference to how many carrier proteins (one or several) were being tested by each manufacturer, not how many were in a single vaccine.

That one of ordinary skill in the art would understand Klein's statement in this manner is manifested by reading the statement in the context of the entire Klein paper and the knowledge of those of ordinary skill at the time of the present invention. On p. 53 of Klein, in the section entitled, "Laboratory and Clinical Studies," Klein describes Table 6 as presenting vaccines currently in development. All are vaccines having a single carrier protein. But, as noted above, some manufactures (e.g., Praxis) were pursuing vaccines with a single type of carrier protein while others (e.g., Pasteur/Merieux/Connaught) were using multiple carriers in the development of their vaccines, each vaccine with a different (but only one) carrier.

Furthermore, had Klein intended to refer to multiple carriers in a single vaccine, one would have expected a more elaborate discussion of it rather than merely a passing mention given that Klein is a review article discussing all aspects of pneumococcal conjugate vaccines and the use of multiple carriers in a single vaccine would have been an a noteworthy feature.

In addition, a 2002 review of the state of pneumococcal vaccines by Wuorimaa and Kayhty (Scand. J. Immunol. **56**, 111-129 (2002); copy enclosed) further supports the view that Klein's statement was not referring to multiple carrier proteins in a single vaccine. Table 1 of Wuorimaa lists numerous pneumococcal conjugate vaccines with 7 to 9 serotypes as referred to by Klein, but all contain only a single carrier protein; Wuorimaa discloses no vaccines with 7 to

9 serotypes conjugated to more than one carrier in a single vaccine.[1] So, Wuorimaa supports the applicants' construction of Klein's statement, too.

The applicants furthermore note that Klein's statement is not a teaching or suggestion to use the particular carrier proteins recited in the present claims, Dt and Tt, together in a single vaccine. This is significant because, as Klein noted (and quoted above), Dt and Tt can "affect carrier priming as a result of prior or co-administration of unconjugated carrier proteins (e.g., diphtheria toxoid) that are often part of other childhood vaccines (e.g., DTP)."

The Office next dismissed the applicants argument that the Israeli and Finnish studies referenced on pp. 3-4 of the specification showed decreased anti-Hib antibody response with increased Dt and Tt load, asserting

> This is not persuasive, because Applicants claims are not so limited and the interference occurred at a total Tt or Dt dose as recited in the claims (1-10 µg of Dt or Tt). *As* such, the claims do not provide for decreased interference as argued and there is no evidence that any of the formulations when combined with the HiB vaccine provides for decreased interference. Dose of carrier protein is a known results effected variable in the conjugate art.

With regard to the assertion that the claims were not so limited (presumably with respect to Hib). the applicants respectfully submit that the ramifications of the Israeli and Finnish studies extend beyond the effects of Dt and Tt on anti-Hib antibody response; they demonstrate that both of these carrier proteins can exert a negative effect on the immunological response to a co-administered polysaccharide conjugate.

With regard to the amount of Dt and Tt, the claims recite that "the amount of Dt in the composition is less than or equal to 60 µg/dose and the amount of Tt in the composition is less than or equal to 25 µg/dose." On page 4 of the specification, the two tables present data demonstrating that the anti-Hib antibody response decreases when combining with increasing amounts of either Dt or Tt in the range of 1 µg – 10 µg, which is within the scope of the present claims. This suggests that the ordinary artisan should *avoid* using Dt and Tt as conjugate carrier proteins as they can lead to decreased immunological response to co-administered polysaccharide even when present in low amounts. At a minimum, these results indicate that

[1] The only examples of the use of multiple carrier proteins in the same vaccine are for 11-valent vaccines and all post-date the present application.

combining various protein carriers and polysaccharide conjugates is to obtain desired results is far from routine or predictable.

The Office next dismissed the applicants' assertion that the Office has not demonstrated that there is a finite number of identified and predictable solutions, arguing that the carrier proteins Dt and Tt were known to the art and successfully used as a carrier in conjugate vaccines. But this manifests hindsight reconstruction of the claims because it ignores the fact that there are numerous proteins that could be employed as carriers, and, as noted above, the results were far from predictable, particularly given the art recognized potential for CIES (discussed above and in the applicants' previous response) and experimental evidence demonstrating that both Tt and Dt can induce CIES (the Israeli and Finnish studies).

Furthermore, the Office's reliance on the "obvious to try" standard of *KSR* is misplaced. That standard is intimately tied to there being a *finite* number of *predictable* solutions. Neither of which elements are present here. At issue in *KSR* was a simple mechanical device and the results of combining the various parts was predictable *a priori*. That is far from the situation for the presently claimed invention.

The Office next dismissed the applicants argument that the compositions are not obvious because it took 100 years to develop such vaccines, responding that it was known to the art that a commercially successful 23-valent pneumococcal vaccine was on the market and the high costs in developing and manufacturing multivalent conjugate vaccines would delay their development by manufacturers. (On several occasions, the Office has responded to the applicants' various arguments that the results achieved by the presently claimed invention were not predictable by noting the existence of the 23-valent vaccine of the '525 application.) The applicants do not understand how the existence of a commerically successful 23-valent pneumococcal vaccine undermines the argument that 100 years have passed since the discovery of conjugate vaccines without the applicants' discovery being implemented. That a single successful multi-valent vaccine exists is not proof that combining any protective antigens in a conjugate vaccine with at least two different carrier proteins is predictable. It is only proof that creating a multi-valent vaccine is not impossible.

Moreover, the applicants respectfully submit that it is patently unreasonable to assert that a 100 year delay is merely the result of high development and manufacturing costs. Such costs are not significantly different than the costs of developing and manufacturing other vaccines and

pharmaceutical drugs and yet numerous vaccines and pharmaceutical drugs have been brought to the market in the last 100 years.

At one point the Office asserted that the combination of multiple carrier proteins as articulated by Merck is obvious. But Merck does not teach a multivalent vaccine employing multiple different carrier proteins.

The Office's main contention appears to be that Dt and Tt were known as carrier proteins, pneumococcal polysaccharides were known as antigens, methods of conjugated the proteins and polysaccharides were known, and the effects of carrier proteins were known. Therefore, the Office contends, the selection of carrier proteins, their dose and the ratio of polysaccharide to carrier proteins, and combination of different carrier proteins was well within the skilled artisan's grasp and making the presently claims composition would amount to no more than mere routine optimization. The applicants disagree with these assertions for several reasons.

First, by asserting that the effects of carrier proteins were known, the Office seems to rely on properties that support the rejection (e.g., the known effect of enhancing immunogenicity of the conjugated polysaccharide) and ignoring factors that refute the rejection (e.g., CIES, which makes formulating vaccines far from routine).

Second, the concept of employing more than one carrier protein was never attempted before. While the act of doing it requires no special skills, it had never been done before (for the various reasons the applicants previously proffered). Although combining different types and numbers of polysaccharides and conjugating them to different protein carriers was commonly known and done, never before had anyone combined two or more carrier proteins, in general, or Dt and Tt, in particular. Accordingly, to characterize combining multiple carrier proteins, in general, and Tt and Dt, in particular, as merely routine optimization is unfair and inaccurate as it ignores 100 years of conjugate vaccine history; combining multiple carrier proteins was simply not in the average artisan's repertoire and, therefore, could not be a part of routine optimization.

Third, the presently claimed compositions represent not merely an optimized composition differing from prior art composition in degree, the presently claimed compositions differ from the prior art in kind. The applicants have not merely combined different protein-polysaccharide conjugates as has been done repeatedly in the prior art, they have, for the first time in the 100 year history of conjugate vaccines, prepared a conjugate vaccine with two or more carrier

proteins in which one is Dt and another is Tt. The result is a composition having high immunogenicity towards the polysaccharide antigens but avoiding or minimizing the effects of CIES. That a composition such as claimed would have this property was unpredictable for the reasons explained above. And because a composition and its properties are inseparable (*In re Papesch*), the presently claimed composition is not obvious.

Fourth, and finally, the Office's position that the presently claimed invention is obvious because it is a mere optimization of routine parameters does not square with case law. In *In re Kubin*, case no. 2008-1184 (Fed. Cir. decided April 3, 2009), the Federal Circuit reiterated the law set forth in *In re Farell* 853 F.2d 894, 895-99 (Fed. Cir. 1988) concerning the "obvious to try" standard in view of *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398 (2007). In particular, the court reemphasized that the sort of "optimization" of parameters the Office asserts renders the present claims obvious is not permitted. In particular, the court stated that,

> [if] what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful,

then the claimed subject matter is not obvious. *In re Farell*, 853 F.2d at 903. The applicants respectfully submit that not only did the prior art not give any indication which parameters were critical nor provide direction of the many possible choices would likely produce a successful vaccine, including not suggesting the use of multiple carrier proteins in a single conjugate vaccine, as noted above the prior art warned of the inherent problems associated with carrier proteins to which a subject had previously been exposed. The prior art cautioned that both Tt and Dt, in particular, were problematic for use as carrier proteins because of their presence in the ubiquitously used DTP vaccine. Thus, not only did the prior art not provide any guidance leading the ordinary artisan to employ Dt and Tt as a carrier proteins in a single vaccine, its teachings would have led the ordinary artisan away from them. The sort of "optimization" on which the Office bases this obviousness rejection is inconsistent with *In re Farell*.

In view of the foregoing amendments and remarks, the Applicants submit that Chu and the '525 publication do not render obvious the presently pending claims. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).

Claims 1-7 and 12-31 remain rejected as obvious over Ahman *et al.* (Pediatr. Infect. Dis. J. 15:134-9, 1996) in view of Anderson *et al.* (J. Pediatr. 128:649-53, 1996) as applied to claims 1, 2, 4, 6, 7, and 14 supra and further in view of the '525 publication. Applicants respectfully traverse this rejection.

The basis for this rejection is essentially the same as before, and the applicants response is therefore the same. The combination of Ahman and Anderson in view of the '525 published application fails to render claims 1-7 and 12-31 obvious for the very same reasons claims 1-7 and 12-31 are not obvious over Chu in view of the '525 published application.

In this rejection, as in the previous rejection, the Office asserts that the '525 published application teaches a composition of conjugates comprising two different types of carrier proteins. The applicants believe it does not. The '525 publication consistently describes compositions containing a single carrier protein.

Therefore, Applicants submit that Ahman, Anderson, and the '525 publication do not render obvious the invention of claims 1-31. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).

Rejection of claims 1-7, 12-15 and 24 under 35 U.S.C. 112, first paragraph

Claims 1-7, 12-15 and 24 were rejected for failing to comply with the written description requirement. The Office asserts that the specification does not describe a composition comprising "one or more dosages of a vaccine" in a manner so as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention. had possession of the claimed invention. The applicants respectfully traverse.

On page 5 of the specification, ll. 15-36, the applicants describe a vaccine composition in which the "quantity of Dt and Tt is respectively less than or equal to 200 and 50 µg/**dose**." (Emphasis added.) And at p. 8, ll. 12-21, the specification states:

> In particular, as regards the diphtheria toxoid and the tetanus toxoid, it is estimated that, advantageously, the quantity of these proteins present in a **dose** of a composition according to the invention should not exceed 200 and 50 µg respectively, such a **dose** being envisaged for administration in a mammal, preferably a human. Preferably, the Dt load is less than or equal to 150, 120 or 100 pg, most preferably 80 20 or 60 µg. Preferably, the Tt load is less than or equal to 35 or 25 µg, most preferably 20 or 10 µg

(Emphasis added.) And the paragraph bridging page 11-12 discusses administration of one or several doses and that a dose of the composition may be in a volume of 0.1 to 2 ml. The applicants respectfully submit that these passages reasonably convey to the ordinary artisan that the applicants had contemplated dosage forms of the presently claimed compositions reciting the specified amounts of Dt and Tt.

In view of the foregoing, the applicants respectfully request reconsideration and withdrawal of this rejection.

In light of the above remarks, Applicants submit that the present application is in condition for allowance and respectfully request notice to this effect. The Examiner is invited to contact Applicants' representative below if any questions arise or he may be of assistance to the Examiner.

Respectfully submitted,

Date: April 6, 2009

/Michael S. Greenfield/
Michael S. Greenfield
Registration No. 37,142

McDonnell Boehnen Hulbert & Berghoff LLP
300 South Wacker Drive
Chicago, IL 60606

Telephone: 312-913-0001
Facsimile: 312-913-0002